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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,874	11/03/2003	Arthur Kunz	AM100788 P1	4900

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/699,874	KUNZ ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *150-256* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *150-164, 167-210, 213-233, 236-256* is/are rejected.

7)☒ Claim(s) *165,166,211,212,234 and 235* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/15/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/15/2008 has been entered.

Election/Restrictions

The Election filed on 11/20/2008 in response to the Restriction Requirement of 10/28/2008 has been entered. Applicant's election, without traverse, of residues 50-66 of SEQ IDNO: 27 as the species for CDR-H2 to be examined has been acknowledged.

Residues 50-66 of SEQ ID NO: 27 for the CDR-H2 appears to be free of the prior art and in view of the other species being free of the prior art, the species requirement has been withdrawn.

Claims 150-256 are currently pending and under consideration.

Claim Objections

Claims 174, in part, 175-180 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, independent claim 173, which all the above claims depend, is drawn to an anti-CD22 antibody comprising a light variable region having a sequence set forth in SEQ ID NO: 28 and a heavy chain variable region having a sequence set forth in SEQ ID NO: 30. Claims 174, in part, 175-180 attempt to further limit the antibody by reciting that the antibody is a monoclonal, chimeric, a human antibody ect. (claim 174), a humanized antibody (claim 175) comprising a variable domain comprising human acceptor framework regions and non-human donor CDR's, e.g., grafted (claims 176-180). However, the specification teaches that SEQ ID NO: 28 is the full sequence of grafted light chain and SEQ ID NO: 30 is the full length sequence of grafter heavy chain (see sequence listing). Moreover, the specification teaches that this antibody is a grafted humanized antibody (see specification page 20, Example 2). As such,

the antibody already appears to contain the light chain variable regions and all of the framework regions.

Appropriate correction is required.

If Applicants were to disagree with the Examiners interpretation, in view of the specification, of SEQ ID NO: 28 and 30, the Examiner requests clarification as to what SEQ ID NO: 28 and 30 encompass.

Claim Rejections - 35 USC § 112

Claims 154-157, 177-180, 200-203, 223-226, 244-247 and 253-256 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, the claims, as set forth above, attempt to further limit the human acceptor framework regions and non-human donor CDR's to regions based on specific sequences. For example, dependent claim 154 recites "wherein the human acceptor framework regions of the variable domain of the heavy chain of the antibody are based on SEQ ID NOS: 21 and 22 and comprise donor resides at positions 1, 28, 48, 72 and 97 of SEQ ID NO: 8. However, it is unclear whether the human acceptor framework regions of the variable domain of the heavy chain of the antibody, in this example, comprise SEQ ID NOS: 21, 28 and 8 or are merely used as templates in view of the term "based". Similar analysis can be applied to the claims which attempt to limit the framework regions of the variable domain of the light chain.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 173-195 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Independent claim 173, which all the above claims depend, recites the limitation "anti-CD22 antibody comprising a light variable region having a sequence set forth in SEQ ID NO: 28 and a heavy chain variable region having a sequence set forth in SEQ ID NO: 30". Thus, the claim limitation implies that the light chain variable region is SEQ ID NO: 28 and the heavy chain variable regions is SEQ ID NO: 30. However, upon careful review of the specification as originally filed, SEQ ID NOS: 28 and 30 represent the full length grafted light and heavy chain (see for example figure 16). Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06.

150-256

Claims 150-164, 167-187, 190-210, 213-233, 236-256 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a subject with a B-cell malignancy which expresses CD22 such as leukemia or lymphoma comprising administering a therapeutically effective dose of a composition comprising a therapeutically effective dose of a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate, does not reasonably provide enablement for a method of treating a subject with any and/or all B-Cell malignanices including those which do not express CD22 comprising administering a therapeutically effective dose of a monomeric cytotoxic drug deriviative/anti-CD22 antibody conjugate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative

skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of treating a B-cell malignancy in a mammal comprising administering a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of treating a subject with a B-cell malignancy comprising administering a therapeutically effective dose of a monomeric cytotoxic drug deriviative/anti-CD22 antibody conjugate. Thus, the claims encompass treating any and/or all B-cell malignancies including those which do not express CD22.

Guidance in the specification and Working Examples

The specification teaches that conjugates of the invention comprise a cytotoxic drug derivatized with a linker that is reactive with a proteinaceous carrier to form a cytotoxic drug derivative-proteinaceous carrier conjugate (page 21, lines 3-5). The specification further teaches that proteinaceous carriers include antibodies which are reactive against a cell surface antigen on B-cell malignancies (page 21, lines 9-10). For example, the specification teaches that antibodies reactive with B-cell malignancies include, without limitation, antibodies directed against CD22 such as G5/44 which is over-expressed on most B-cell lymphomas (page 22, lines 25-27). As such, the specification teaches that the these antibody conjugates are useful for the treatment of proliferative disorders namely lymphomas and leukemias, which express CD22 antigen on the cell surface; and further, provides a plethora of lymphomas and leukemias contemplated for treatment (page 40, lines 1-20). Thus, while the specification reasonably conveys a method of treating a proliferative disorder namely lymphoma or leukemia which express a CD22 antigen with the anti-CD22 conjugate, the specification appears to be silent on a correlation between the anti-CD22 antibody conjugate and the treatment of any and/or all cancers including carcinomas and sarcomas. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of in vitro

findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that anti-CD22 antibodies, as well as the immunoconjugates thereof, are useful for the treatment of B-cell malignancies. For example, Goldenberg et al. (US 6,183,744, 2001, of record) teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent (column 4, lines 25-26 and column 11, lines 5-8). Moreover, Goldenberg teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14). In addition to Non-Hodgkin's lymphoma, Goldenberg et al. teaches that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias, and acute lymphatic leukemias (column 11, lines 8-11). Similarly, Uhr et al. (US 5,686,072, 1997, of record) teach a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of a combination of an anti-CD19 antibody and anti-CD22 immunotoxin, wherein the B cell malignancy includes, but is not limited to, leukemia and non-Hodgkin's lymphoma (column 2, lines 48-54 and column 6, lines 16-21). Thus, while the state of the prior art suggests a correlation with CD22 and B-cell malignancies, the prior art appears to be silent on CD22 expression being associated with carcinomas and sarcomas.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claims 243-247 be found allowable, claims 252-256 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 165-166, 211-212 and 234-235 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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